Dig Dis Sci (2009) 54:1050–1058
DOI 10.1007/s10620-008-0456-y

ORIGINAL ARTICLE

# Detection of Neuroendocrine Tumors of the Small Bowel by Double Balloon Enteroscopy

**Michael Bellutti · Lucia C. Fry · Johannes Schmitt · Marcus Seemann · Silke Klose · Peter Malfertheiner · Klaus Mönkemüller**

Received: 26 May 2008 / Accepted: 16 July 2008 / Published online: 4 September 2008


**Abstract** *Background* Neuroendocrine tumors (NET) account for one-third of all small bowel neoplasms. The search for the primary tumor in NET is important, even though it is difficult to localize, as its surgical excision leads to a better prognosis, even in metastasized stages of the disease. The objective of this study was to evaluate the use of double balloon enteroscopy (DBE) for the detection of the primary tumor in patients with NET. *Methods* Twelve consecutive patients (eight women, four men) with suspected carcinoid syndrome, either metastatic to the liver ($n = 5$), symptoms of a neuroendocrine tumor with elevated tumor markers ($n = 5$), or obscure gastrointestinal bleeding ($n = 2$) underwent DBE for the search of the primary tumor or the source of bleeding. All patients underwent abdominal sonography and a computed tomography (CT) scan, esophagogastroduodenoscopy (EGD), ileocolonoscopy, and octreotide scintigraphy prior to DBE. Capsule endoscopy was performed in four patients. *Results* A total of 17 DBE were performed in the 12 patients. The CT scan and sonography of the abdomen as well as EGD and ileocolonoscopy were unable to detect the primary tumor in any patient. A submucosal tumor of the ileum or the jejunum could be detected by DBE was detected in seven patients (58%) (anal route, $n = 4$; oral route, $n = 3$). In four of these patients (33%) this finding could be confirmed by the surgical resection of a NET. In two patients (17%) with a submucosal ileum protrusion suspicious for NET, laparotomy and intraoperative endoscopy did not confirm the tumor. *Conclusions* In this study, the diagnostic yield of DBE for primary tumor search in patients with metastatic or suspected NET was 33%. Although endoscopic small bowel investigation by DBE seems to enrich the diagnostic possibilities for the diagnosis of small bowel-NET, at the present time DBE should only be performed in selected cases, possibly based on a positive previous work-up.

**Keywords** Double balloon enteroscopy · Intestinal disorders · Neuroendocrine tumors · Small bowel

Michael Bellutti and Lucia C. Fry contributed equally to this paper.

M. Bellutti · L. C. Fry · P. Malfertheiner · K. Mönkemüller (✉)
Department of Gastroenterology, Hepatology and Infectious Diseases, Universitätsklinikum, Otto-von-Guericke University, Leipziger Strasse 44, 39120 Magdeburg, Germany
e-mail: Klaus.Moenkemueller@med.ovgu.de

J. Schmitt
Institute of Pathology, Universitätsklinikum, Otto-von-Guericke-University, Magdeburg, Germany

M. Seemann
Department of Radiology and Nuclear Medicine, Universitätsklinikum, Otto-von-Guericke-University, Magdeburg, Germany

S. Klose
Department of Endocrinology and Metabolism, Universitätsklinikum, Otto-von-Guericke-University, Magdeburg, Germany

## Introduction

Neuroendocrine tumors (NET) account for about one-third of all small bowel neoplasms. Even NET of a small size can metastasize to the lymph nodes and liver [1, 2]. Small bowel-NET arise from enterochromaffin cells and, due to their endocrine function, may induce symptoms such as diarrhea, flushing, and sweating. Gastrointestinal (GI) bleeding, obstruction, and/or perforation are derived from local complications at the site of primary tumor involvement in the small bowel [3]. Because of the non-specific

initial symptoms of NET, patients are often correctly diagnosed only in advanced, metastasized stages of the disease, when a curative therapeutic option is beyond practicability [2, 4]. The search for the primary tumor is often cumbersome, but of crucial importance, as its surgical excision leads to a better prognosis, even in metastasized NET [4, 5]. With conventional imaging techniques, such as enteroclysis, the detection of the primary tumor of small bowel-NET is difficult because of its small size and the possibility of assessing only the luminal part of the small bowel [6]. Octreotide scintigraphy is an approved method with a high diagnostic yield for detecting both early and advanced stages of NET, but due to its two-dimensional view, the differentiation between mesenteric and intestinal localization is not possible and in the case of low receptor density, NET might not be detectable [7]. However, current guidelines recommend abdominal ultrasound, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the upper and lower abdomen as well as octreotide scintigraphy and small bowel enteroclysis for the detection of the primary tumor in the small bowel [1].

Preliminary evidence suggests that investigating the small bowel by capsule endoscopy (CE) may facilitate the identification of a primary tumor in patients with carcinoid syndrome or metastatic NET [8, 9]. Double balloon enteroscopy (DBE) permits evaluations of the small bowel to be carried out and has become a valuable diagnostic and therapeutic tool in many diseases that up to recent times were under diagnosed or could not be treated endoscopically [10–13]. An advantage of DBE is the possibility to take targeted biopsies from suspicious lesions. Although a recent case report described the use of DBE for the diagnosis of small bowel-NET in one patient, the role of DBE in the evaluation of small bowel tumors and NET is as yet unknown [14]. The aim of our study was to evaluate the utility of DBE in detecting the primary tumor in patients with suspected NET or with liver metastases of a NET.

## Methods

Double balloon enteroscopy was performed between May 2005 and July 2007 in a group of 12 patients included in a prospective database. These patients were referred for primary tumor search based on an indication of carcinoid syndrome, with five patients showing histologically proven metastases to the liver and five showing carcinoid syndrome with elevated levels of chromogranin A and serotonin. Of these latter five patients, three had been previously operated for a cecal or small bowel-NET, and two had classical carcinoid syndrome based on clinical and laboratory parameters. In two patients with a NET, DBE was performed because of chronic GI bleeding in the absence of other systemic symptoms. All patients underwent abdominal sonography and a CT scan, esophagogastroduodenoscopy (EGD), and ileocolonoscopy as well as octreotide scintigraphy prior to DBE. Capsule endoscopy was performed on four patients.

The study was conducted in accordance with the Helsinki Declaration (1989 revision), and approval was given by our institutional review board. Patients provided written informed consent to undergo DBE, which was performed using a therapeutic Fujinon enteroscope (model EN-450 T5/20; Fujinon, Omiya, Japan). The depth of scope insertion was calculated based on the method described by May et al. [13]. Small-bowel cleansing was done the day before the procedure by means of 4 l of a standard colon lavage solution (Klean-Prep; Norgine GmBH, Marburg, Germany). Conscious sedation of the patient using midazolam and disoprivan was used in all cases, with a second physician assisting the procedure. Butyl-scopolamine (Buscopan; Boehringer Ingelheim, Ingelheim, Germany) was used to relax small bowel motility, if necessary, for a more precise investigation. Biopsies were performed in all cases where a tumor or protrusion of the small bowel could be detected using a Fujinon forceps (FTE, F6BBPK1802250, 1.8 mm in diameter; Fujinon, Willich, Germany). At least six biopsies were obtained from each lesion. India ink (Sterimark, Life Partners Europe, Bagnolet, France) was injected to mark the tumor site in order to facilitate intraoperative detection of the primary tumor. Small bowel biopsies were fixed and preserved in 10% formalin for histopathological and immunohistochemical evaluation. Special stains were used for chromogranin A, serotonin, synaptophysin, and Mib1, and the Ki-67 proliferation index was calculated. All patients followed strict dietary and physical activity instructions during the 2 days prior to the measurement of chromogranin A: the ingestion of banana, nuts, kiwis, tomatoes, vanilla, plums, and coffee was avoided in this period; nicotine use was not allowed; strenuous exercise or sport was avoided. The patients were also not allowed to use the following medications: theophylline, methyldopa, L-dopa, paracetamol and non-steroidal anti-inflammatory drugs.

A suspicious NET was defined as the presence of a yellowish submucosal tumor covered either by normal appearing mucosa or with signs of exulceration, or by compression from outside the small bowel lumen. A certain diagnosis was defined as the histological confirmation of a NET. The diagnostic yield was calculated based on histologically confirmed cases of NET.

Patient's characteristics, endoscopic and histological findings, and diagnostic and therapeutic outcomes are presented using descriptive statistics with means and ranges.

## Results

A total of 17 DBE (oral route = 9, anal route = 8, one patient had two oral DBE) were performed in the 12 patients (eight female, four male; mean age 62 years, range 43–75 years). Four and three patients were investigated using only the oral or anal approach, respectively, and five patients were investigated by combined oral and anal DBE. The mean duration for oral DBE was 60 min (range 45–90 min) and that for anal DBE was 59 min (range 45–90 min). The patient's clinical characteristics, endoscopic findings, and results from additional investigations are presented in Table 1. The CT scan and sonography of the abdomen, the EGD, and the colonoscopy were unable to detect the primary tumor in any patient.

A submucosal tumor of the ileum or the jejunum protruding into the lumen could be detected by DBE in seven of the 12 patients (58%; patients 1, 3, 5, 7, 9, 11, 12); anal DBE led to this finding in four patients (3, 9, 11, 12) with a tumor in the ileum, and oral DBE was useful in detecting the tumor in the distal jejunum or proximal ileum in three patients (Fig. 1; patients 1, 5, 7). In five patients, DBE was not successful in detecting a small bowel tumor suspicious of a NET. In four of the seven patients (33.3%) with a positive finding in the DBE, a NET was confirmed by surgical resection and pathological examination (Fig. 2a–d; patients 1, 5, 7, 11). The mean depth of insertion was 288 cm distal to the pylorus (range 280–420 cm) for oral DBE and 52 cm from the ileocecal valve (range 20–120 cm) for anal DBE. Total small bowel inspection was achieved in only one patient (no. 8).

The CE normal in one patient (no. 12) of the four patients (nos. 2, 5, 7, 12) who underwent this test and abnormal in three, with multiple ulcers of the ileum in patient 5 and submucosal tumors of the jejunum in patients 2 and 7. In patients 5 and 7, tumors of the ileum and jejunum were confirmed by DBE (Fig. 3). The CE was false positive (with respect to DBE) in patient no. 2, where no primary tumor could be detected using various other investigation modes (DBE, octreotide scintigraphy).

Octreotide scintigraphy was positive in projection to the liver in all five patients with liver metastases (patients 2, 3, 7, 9, 11). In one patient, octreotide scintigraphy was also positive in projection to the stomach, but without any endoscopic correlative (patient 6). An enhancement in projection to the site of the primary tumor was found in three patients (Fig. 4; patients 5, 7, 11).

Multiple ulcerated tumors of the jejunum could be diagnosed by oral DBE in two patients (Fig. 5; patients 1, 5), one of whom was found to have a bleeding lesion (Fig. 6; patient 1). Anal DBE of another patient revealed a protrusion into the terminal ileum that was 2 cm in diameter, with central erosion; this was confirmed as a NET after surgery (Fig. 7a, b; patient 11). In none of these three patients did biopsies obtained during DBE demonstrate a NET.

In total, six of seven patients with suspicious NET underwent surgery, and the presence of NET was confirmed in four cases (patients 1, 5, 7, 11). In two patients, the results of the DBE turned out to be false positives, as there was not detection of a NET intraoperatively (patients 3, 9). One of these patients with a submucosal ileum protrusion underwent diagnostic laparotomy with additional intraoperative enteroscopy without confirmation of a NET (patient 3). The seventh patient did not undergo surgery because of her comorbidities and a protracted recovery after previous surgery (patient 12).

## Discussion

To the best of our knowledge, there are no previous reports describing the diagnostic yield of enteroscopy or DBE in NET. In our study, the diagnostic yield of DBE in a tumor search in patients with proven or suspected NET was 33%. Double balloon enteroscopy was able to detect a submucosal tumor of the jejunum or ileum in seven of the 12 patients; in four cases this finding was confirmed by the surgical resection of a NET, and in two patients, the DBE result was a false positive.

Although DBE has the potential advantage over CE of allowing tissue retrieval, in none of our patients did biopsy reveal a NET. Possible explanations for this result include (1) technical problems, (2) superficiality of biopsies, and (3) submucosal localization of the tumor. Other potential reasons for not finding the tumor could be the localization of NET in non-visualized parts of the small bowel or the common mesenterical localization of NET. Additionally, the failure to achieve deep ileal intubation during anal DBE could explain the comparatively low diagnostic yield. The high number of incomplete enteroscopies may have been due to several potential factors, such as fixed small bowel/abnormal anatomy, type of DBE-scope used, and inadequate time. In addition, the first cases were performed with the diagnostic enteroscope, whereas subsequent cases were performed with the therapeutic DBE. The diagnostic DBE scope has a smaller diameter and is floppier, which makes it more difficult to manipulate. Our findings may have clinical implications by demonstrating that anal DBE may not be an adequate test to search for NET. As such, the diagnostic information obtained by searching for small bowel-NET using CE may be at least as good as that made available by DBE. Whereas oral DBE achieved a mean depth of inspection of 288 cm distal to the pylorus, mean ileal intubation was only 52 cm from the ileocecal

**Table 1** Clinical patient's characteristics

| Number | Age (years) | Sex | Indication | Endoscopic findings/histological findings | Oral/anal route—depth of insertion | Octreotide scintigraphy | Additional investigations | Chromoogranin A (< 110 μg/l) | Therapy/outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 48 | F | OGIB suspicion of liver metastases | Jejunal ulcers/histology | Oral: 320 cm | Negative | EGD, colonoscopy, abdominal US, CT-abdomen and thorax | 656 | Surgery, resection of a NET of the ileum; octretotide i.m. 4-weekly |
| 2 | 62 | F | Liver metastases of a NET; jejunal polypoid lesions on CE | No pathological finding | 1. Oral: 280 cm<br>2. Oral: 420 cm<br>Anal: 60 cm | Enhancement in the liver | CE; abdominal CT-scan and US, EGD, colonoscopy | 9,300 | Octreotide LAR i.m. 4-weekly/progression after 6 Months |
| 3 | 69 | M | Liver metastases of a NET | Submucosal tumor of the terminal ileum, 3 × 4 cm in size/2 biopsies negative | Anal: 25 cm | Enhancement in the liver and left upper abdomen | EGD, colonoscopy, abdominal US, CT-abdomen and thorax | 2,090 | Diagnostic laparotomy, no primary tumor detected; octreotide i.m. 4-weekly; 90-Y-dotatoc-therapy after progression |
| 4 | 52 | F | Elevated gastrin, chromogranin A and serotonin; persisting diarrhea | No pathological finding | Oral: 300 cm | No pathological finding | Abdominal US, EGD, colonoscopy, pancreatic endosonography | 1,185 | No NET on follow-up |
| 5 | 68 | M | OGIB; ulcerative lesions in CE; suspicion of two liver metastases | two ulcerated submucosal tumors, 1 and 3 cm, in the proximal ileum, histology negative | Oral: 250 cm ab ore (BII-stomach)<br>Anal: 5 cm | Enhancement in the lower abdomen | EGD, colonoscopy, CE, MRI-enteroclysis, CT-abdomen and thorax | NP | Surgery, resection of a NET of the ileum |
| 6 | 59 | F | Flush, diarrhea, elevated chromogranin A | No pathological finding | Oral: 300 cm | Enhancement in the stomach/ duodenum | Abdominal US, EGD, colonoscopy, MRI, MRI-enteroclysis, pancreatic endosonography | 364 | −/follow-up 1 year: no primary tumor detected |
| 7 | 55 | M | Liver metastases of a NET; submucosal tumor with central lymphangiectasias in CE | 8 mm polypoid jejunal lesion with central lymphangiectasias/no biopsies | Oral: 250 cm<br>Anal: 50 cm | Enhancement in the liver and the left lower abdomen | CE, EGD, colonoscopy, abdominal US, CT-abdomen and thorax | 1,030 | Surgery, resection of a NET of the jejunum/octreotide LAR i.m. 4-weekly |
| 8 | 60 | F | Flush and diarrhea after resection of a NET of the terminal ileum | No pathological finding | Oral: 280 cm<br>Anal: 120 cm (from ileocecal anastomosis) | Negative | CT-abdomen and thorax; abdominal US, EGD, colonoscopy | <110 | Octreotide i.m. 4-weekly/no relapse |
| 9 | 43 | F | Liver metastases of a NET | Protrusion into the lumen of the terminal ileum | Anal: 120 cm | Enhancement the liver | EGD, colonoscopy, CT Abdomen and thorax; abdominal US | 1,040 | Ileum resection, peritoneal carcinosis; octreotide i.m. 4-weekly/ progression after 1 year |

**Table 1** continued

| Number | Age (years) | Sex | Indication | Endoscopic findings/histological findings | Oral/anal route—depth of insertion | Octreotide scintigraphy | Additional investigations | Chromoogranin A (< 110 µg/l) | Therapy/outcome |
|---|---|---|---|---|---|---|---|---|---|
| 10 | 66 | M | Staging after resection of duodenal and cecal NET; increased chromogranin A | No pathological finding | Oral: 300 cm | No pathological finding | Abdominal US, EGD with mucosectomy of duodenal NET; endosonography | 286 | No relapse or NET again |
| 11 | 70 | F | Liver metastases of a NET | Tumor of the terminal ileum with central erosion, 2 cm in diameter/biopsy failed for technical reasons | Anal: 20 cm | Enhancement in the liver and the terminal ileum | EGD, colonoscopy, abdominal US, CT abdomen and thorax | 12,500 | Surgery, resection of a NET of the terminal ileum; octreotide i.m. 4-weekly; J-131-MIBG radiotherapy; liver metastases regressive after 1 year |
| 12 | 75 | F | Staging after resection of a NET-metastasis of the mesenteric radix | 1 × 2 cecal lesion without mucosal alterations | Oral: 180 cm<br>Anal: 20 cm | Enhancement the mid/lower abdomen | EGD, colonoscopy, MRI, CT-enteroclysis, CE negative | 137 | Follow-up without therapy |

F, Female; M, male; OGIB, Obscure GI bleeding; CE, capsule endoscopy; NET, neuroendocrine tumor; EGD, esophagogastroduodenoscopy; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; LAR, long-acting release; i.m., intramuscular

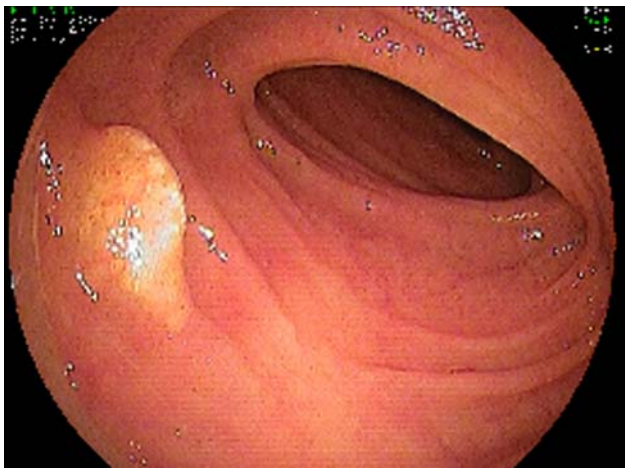

**Fig. 1** Submucosal polypoid tumor of the distal jejunum emerging to be a neuroendocrine tumor (NET) after surgical resection

valve. In four patients, a mean ileal intubation of only 17.5 cm was possible. This appears to be a problem that is frequently encountered when performing anal DBE and is not only specific to our center, as recent studies from the USA demonstrate a failure to intubate the ileum in up to 30% of patients [15]. As NET of the small bowel are found mainly in the ileum, the anal approach of DBE can be considered to be superior to oral DBE for this indication [2, 16–18]. In our series, only the oral approach was selected in four patients because previous tests, such as CT or ultrasound, had shown suspicious small bowel lesions in the jejunum. The same was true for choosing the anal approach. In five patients, where no primary tumor was detected using other imaging techniques, both anal and oral DBE were performed. Nevertheless, the technical problems that often occur during anal DBE with prolonged examination times, such as unsuccessful intubation of the terminal ileum and, in the case of successful intubation, visualization of only a short segment of the distal ileum, seem to be limiting factors. Based on the results of our study, it does not seem to be distinctly necessary to perform both oral and anal DBE for the detection of small bowel-NET from the beginning of the diagnostic work-up: of six patients undergoing surgery for a positive finding in DBE, three suspicious tumors were detected by oral DBE in the mid or distal jejunum and in the proximal ileum. In each of these cases, the finding could be confirmed by resection of a NET. To the contrary, only in one patient with a positive finding in anal DBE could a NET be confirmed by surgery. It must be also be mentioned that in this last case, because of its location in the terminal ileum, this NET could have potentially been detected by ileocolonoscopy.

Ink injection can be considered to be a valuable method that facilitates the detection of the primary tumor intraoperatively, as shown in two patients where this technique

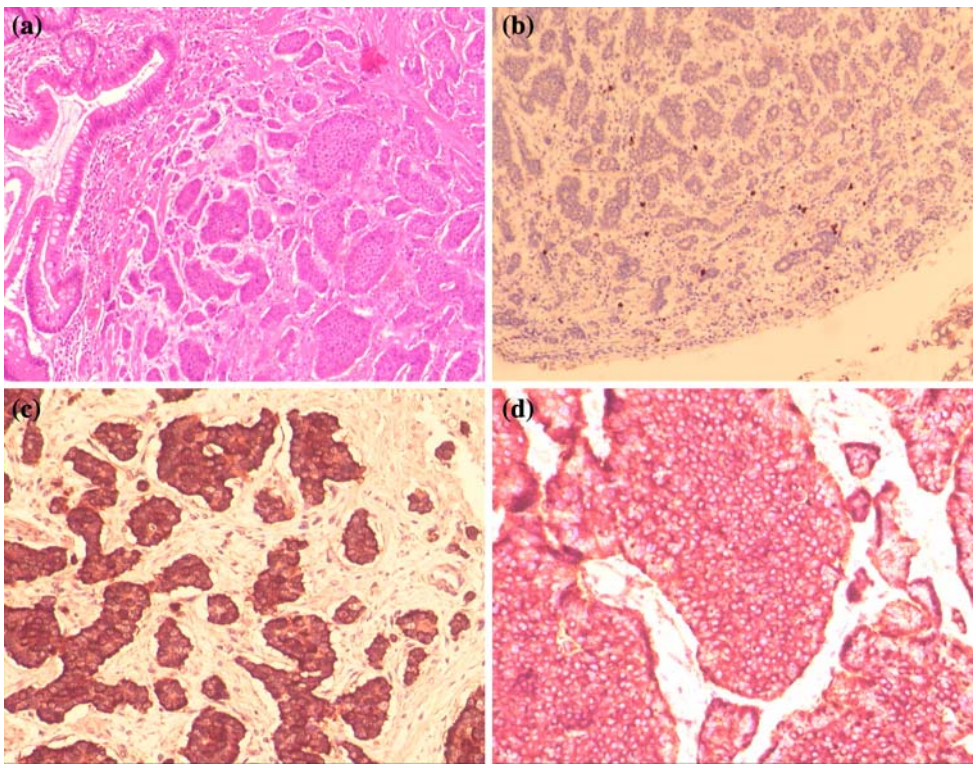


**Fig. 2** Histological examination of a NET in the surgical preparation. (**a**) Hematoxylin–eosin stain, magnification 25×, (**b**) immunohistochemical Mib-1 stain, Ki-67 index <1%, (**c**) immunohistochemical staining with anti-chromogranin A, (**d**) pronounced immunohistochemical staining with anti-serotonin antibodies

**Fig. 3** Capsule endoscopy (CE) image of the NET pictured in Fig. 1

was applied. This technique has also been described for other indications, such as bleeding from angiodysplasias with subsequent surgery [19, 20]. Given the remarkable easing effect on subsequent surgery, this property makes DBE superior to CE for this indication.

A recent study using CE by van Tuyl et al. obtained a diagnostic yield of 45% (nine of 20 patients) for detecting NET of the small bowel [9]. Similar to our study—not all patients underwent surgery in van Tuyl et al.'s series—the number of false positive findings could not be ascertained, and the true diagnostic yield remains unknown. Additionally, the study by van Tuyl et al. clearly highlights the difficulty in carrying out a luminal tumor search in NET, as in seven patients with positive octreotide scintigraphy, the CE was negative for a supposed mesenteric localization of the NET. Another study comparing CE- to CT-enteroclysis underlines this point [8]: of eight patients, the primary tumor could be detected by CE in three patients and by CT-enteroclysis in four patients. The authors conclude that the frequent extraluminal growth could be a limiting factor for CE. Octreotide scintigraphy and CT-enteroclysis are established methods for the detection of small bowel-NET. Nevertheless, its use for the exact localization of the tumor in the preoperative diagnostic pathway is limited [21]. There are no studies evaluating the usefulness of intraoperative enteroscopy for the search of NET of the small bowel. Due to its ability to inspect the entire small bowel both luminally and extraluminally, with the additional advantage of the surgeon being able to palpate for submucosal lesions, we assume that intraoperative enteroscopy is a potential gold standard for these tumors. Thus, the

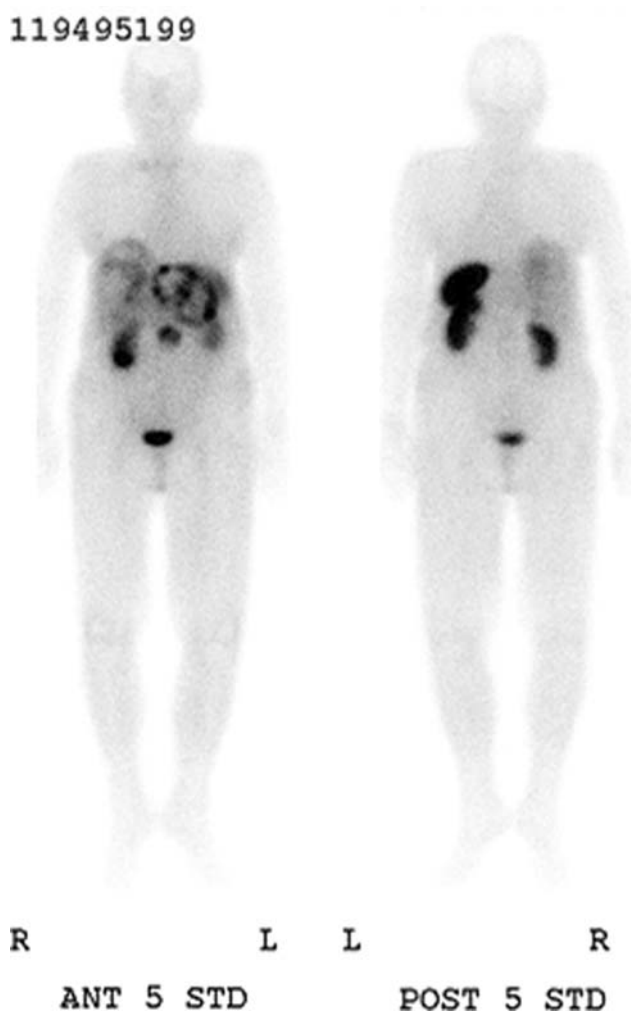


**Fig. 4** Octreotide scintigraphy with tracer-uptake in projection to the terminal ileum and the liver

**Fig. 5** Polypoid submucosal tumor of the proximal ileum with central ulceration

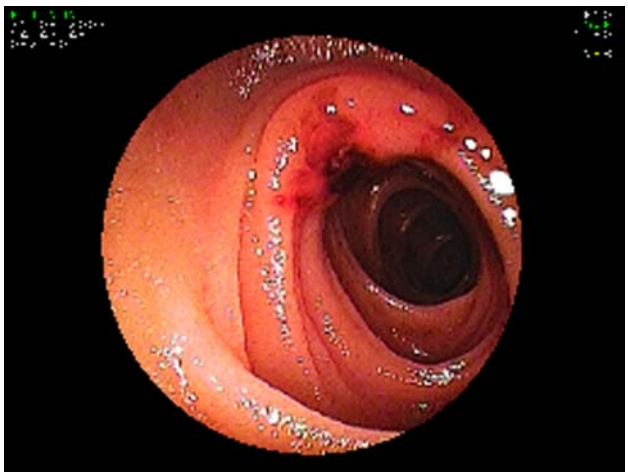

**Fig. 6** Bleeding ulcer of the jejunum diagnosed as NET after resection

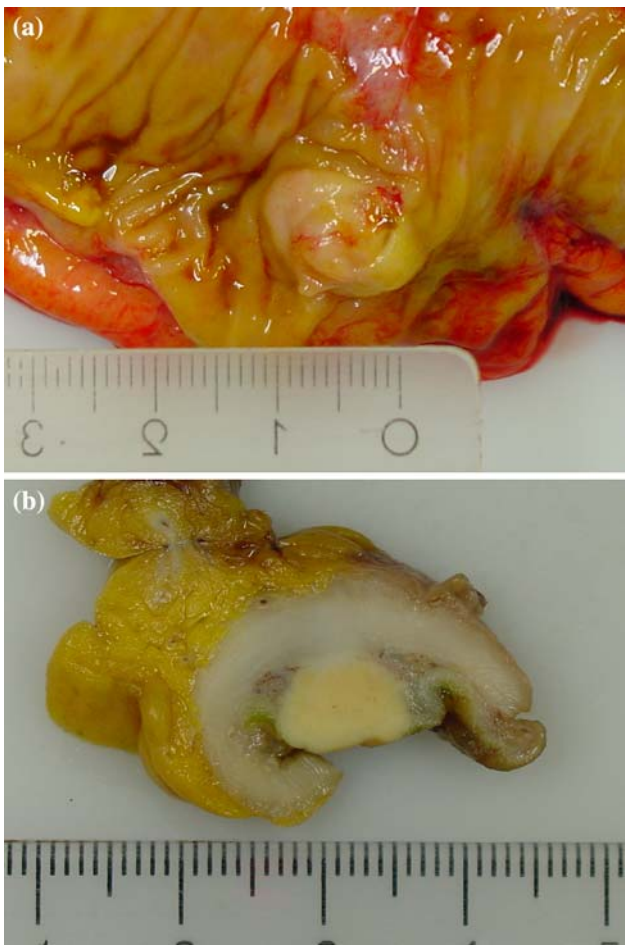


**Fig. 7** (**a**) Macroscopic image of a 1.5-cm NET of the terminal ileum, (**b**) cross-section of the surgical preparation of a 1.5-cm NET of the terminal ileum

utility of intraoperative enteroscopy should be evaluated in future studies in patients with NET, given its potential higher yield.

In our study, biopsies were unable to provide evidence of a NET in any of the patients with a visible tumor of the small bowel, even patients with ulcerated lesions. Possible explanations for this is our use of small-sized forceps during DBE, which do not allow the surgeon to obtain large pieces of tissue (even in ulcerated NET), and/or the submucosal location of the tumor. In the light of our results, the potential advantage of DBE in enabling tissue retrieval has to be reconsidered and, consequently, DBE with biopsy may not be as advantageous—in comparison to CE—for detecting small bowel-NET than previously assumed. In clinical practice, CE with the detection of a small bowel tumor suspicious for being the primary NET in combination with a positive octreotide scintigraphy in projection to the suspected tumor site could be a less invasive method for the detection of the primary tumor. In our study, CE was able to detect the primary tumor in two cases, both of which were confirmed by DBE and by surgery. Capsule endoscopy was not performed in all the patients, as initially it was not available in our institution.

The potential limitations of our study include it small size and the fact that we are a tertiary referral center with a pre-selected collective, although patients with NET are seldom evaluated in primary care centers. Nevertheless, our study is the largest one to date using DBE for evaluating small bowel-NET. In the current era of the new diagnostic methods for small bowel evaluation, such as CE and/or DBE, all reports may have reasonable value. The final goal of such studies is to position diagnostic methods, such as DBE, in the diagnostic algorithm for relatively rare conditions, such as NET.

In summary, endoscopic small bowel investigation by DBE seems to enrich the possibilities for the diagnosis of small bowel-NET. Double balloon enteroscopy seems to be a valuable method, especially in the preoperative setting, due to the possibility of marking the precise site of the tumor by means of ink injection. Before adding this new endoscopic technique to current guidelines, however, larger, multicenter, prospective studies comparing the yield of DBE to CE and to conventional radiological techniques are needed. According to the current standard of knowledge, DBE for the diagnosis of small bowel-NET should only be performed in selected cases, possibly based on a positive previous work-up.

## References

1. Plöckinger U, Rindi G, Arnold R, et al Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology*. 2004;80:394–424.
2. Kulke MH, Mayer RJ. Carcinoid tumors. *N Engl J Med*. 1999;340:858–868. doi:10.1056/NEJM199903183401107.

3. Modlin IM, Latich I, Zikusoka M, Kidd M, Eick G, Chan AK. Gastrointestinal carcinoids: the evolution of diagnostic strategies. *J Clin Gastroenterol*. 2006;40:572–582. doi:10.1097/00004836-200608000-00003.
4. Kerström G, Hellman P, Hessman O. Midgut carcinoid tumours: surgical treatment and prognosis. *Best Pract Res Clin Gastroenterol*. 2005;19:717–728. doi:10.1016/j.bpg.2005.05.005.
5. Boudreaux JP, Putty B, Frey DJ, et al Surgical treatment of advanced-stage carcinoid tumors: lessons learned. *Ann Surg*. 2005;241:839–845. doi:10.1097/01.sla.0000164073.08093.5d.
6. Kaltsas G, Rockall A, Papadogias D, Reznek R, Grossman AB. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. *Eur J Endocrinol*. 2004;151:15–27. doi:10.1530/eje.0.1510015.
7. Nikou GC, Lygidakis NJ, Toubanakis C, et al Current diagnosis and treatment of gastrointestinal carcinoids in a series of 101 patients: the significance of serum chromogranin-A, somatostatin receptor scintigraphy and somatostatin analogues. *Hepatogastroenterology*. 2005;52:731–741.
8. Johanssen S, Boivin M, Lochs H, Voderholzer W. The yield of wireless capsule endoscopy in the detection of neuroendocrine tumors in comparison with CT enteroclysis. *Gastrointest Endosc*. 2006;63:660–665.
9. van Tuyl SA, van Noorden JT, Timmer R, Stolk MF, Kuipers EJ, Taal BG. Detection of small-bowel neuroendocrine tumors by video capsule endoscopy. *Gastrointest Endosc*. 2006;64:66–72.
10. Yamamoto H, Yano T, Kita H, Sunada K, Ido K, Sugano K. New system of double-balloon enteroscopy for diagnosis and treatment of small intestinal disorders. *Gastroenterology*. 2003;125:1556–1557.
11. Heine GD, Hadithi M, Groenen MJ, Kuipers EJ, Jacobs MA, Mulder CJ. Double-balloon enteroscopy: indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease. *Endoscopy*. 2006;38:42–48.
12. Mönkemüller K, Weigt J, Treiber G, et al Diagnostic and therapeutic impact of double-balloon enteroscopy. *Endoscopy*. 2006;38:67–72.
13. May A, Nachbar L, Wardak A, Yamamoto H, Ell C. Double-balloon enteroscopy: preliminary experience in patients with obscure gastrointestinal bleeding or chronic abdominal pain. *Endoscopy*. 2003;35:985–991.
14. Yamaguchi T, Manabe N, Tanaka S, et al Multiple carcinoid tumors of the ileum preoperatively diagnosed by enteroscopy with the double balloon technique. *Gastrointest Endosc*. 2005;62:315–318.
15. Mehdizadeh S, Ross A, Gerson L, et al What is the learning curve associated with double-balloon enteroscopy? Technical details and early experience in 6 U.S. tertiary care centers. *Gastrointest Endosc*. 2006;64:740–750.
16. Horton KM, Kamel I, Hofmann L, Fishman EK. Carcinoid tumors of the small bowel: a multitechnique imaging approach. *Am J Roentgenol*. 2004;182:559–567.
17. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. *Gastroenterology*. 2005;128:1717–1751.
18. Mehdizadeh S, Han NJ, Cheng DW, Chen GC, Lo SK. Success rate of retrograde double-balloon enteroscopy. *Gastrointest Endosc*. 2007;65:633–639.
19. Matsumoto T, Esaki M, Moriyama T, Nakamura S, Iida M. Comparison of capsule endoscopy and enteroscopy with the double-balloon method in patients with obscure bleeding and polyposis. *Endoscopy*. 2005;37:827–832.
20. Su MY, Liu NJ, Hsu CM, Chiu CT, Chen PC, Lin CJ. Double balloon enteroscopy—the last blind-point of the gastrointestinal tract. *Dig Dis Sci*. 2005;50:1041–1045.
21. Ricke J, Klose KJ, Mignon M, Oberg K, Wiedenmann B. Standardisation of imaging in neuroendocrine tumours: results of a European delphi process. *Eur J Radiol*. 2001;37:8–17.